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Study of contribution by *Plasmodium vivax* to malarial morbidity among children hospitalized with severe malaria in a tertiary level hospital of northern India

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Abstract
Background and Objectives: Malaria is one of the most widespread infectious diseases of tropical countries with *Plasmodium falciparum* being the most prevalent malaria parasite in WHO South-East Asia Region (SEAR). However, *Plasmodium vivax* also is now being realized to cause severe life-threatening disease. Objective of this research was to study the profile of severe malaria and contribution of vivax infection to malarial morbidity in North Indian children.
Methods: It is a single centre, prospective, observational study conducted over the period of 1 year in a tertiary level teaching hospital in northern India. All patients of age < 15 years, admitted during the study period with diagnosis of severe malaria, as per World Health Organization (WHO) (2014) criteria, were enrolled in the study. Patients were categorized into either of three groups: P. vivax (Pv) monoinfection, P. falciparum (Pf) monoinfection and mixed P. vivax with P. falciparum infection (Pf+Pv) and were analyzed for clinical and epidemiological profile. Furthermore, contribution of *Plasmodium vivax* to the severe malarial morbidity was studied.
Results: Out of 1880 children screened, 27 children were diagnosed to be having severe malaria. Out of theses, 51.8% (n=14) had P. vivax (Pv) mono-infection, 18.5% (n=5) had mixed infection with both vivax and falciparum and only 29.6% (n=8) had P. falciparum (Pf) mono-infection. Pv patients had much wider age range compared to Pf, though median age was similar in all groups. However, proportion of patients from younger age group (<5 y) was significantly higher in Pv group. The clinical features on admission were similar in all the groups. Duration of illness and hospitalization were also similar in all groups with shorter median duration of symptoms in Pf group. Among various clinical syndromes, severe anemia, cerebral malaria and hepatitis were common to all groups. Severe anemia and shock were more frequently observed in Pf group whereas cerebral malaria, hepatitis, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and bleeding symptoms were more commonly seen in Pv patients.
Interpretation & conclusion: Factors associated with severe malaria and resulting mortality, identified in this study were consistent with other studies. This research shows that severe malaria is still an important cause of morbidity and mortality among young children. It was concluded that vivax malaria is emerging as an important cause of malaria-related complications, including death in children.

Keywords: *Plasmodium falciparum; Plasmodium vivax;* children, severe malaria, cerebral malaria, India

Introduction
Malaria is one of the important public health problems with an estimated 228 million cases of malaria occurring worldwide in 2018, of which 3.4% was contributed by WHO South-East Asia Region (SEAR). Malaria caused 405,000 deaths worldwide in 2018 and 67% (272,000) of these deaths occurred in children aged less than 5 years. *Plasmodium falciparum* (Pf) is the predominant species worldwide, accounting for around 50 % of cases in WHO South-East Asia Region [1]. In India, incidence of malaria is gradually declining from 2.08 million in 2001 to 0.84 million in 2017. Of these 0.84 million cases in 2017, 0.53 million were contributed by *Plasmodium falciparum* [2]. Orissa, Chhattisgarh, West Bengal, Jharkhand and Karnataka contribute the most number of cases of malaria in India [3] The biggest burden of malaria in India is borne by the most backward, poor and remote parts of the country, with >90-95% cases being reported from rural areas and only <5-10% from urban area. The proportion of *P. vivax* (Pv) and *P. falciparum* varies in different parts of India; *P. falciparum* accounts for 30–90% of the infections in the forested areas inhabited by ethnic tribes and only for <10% of malaria cases in indo-gangetic plains, northern hilly states, north-western India, and southern Tamil Nadu [4].

Although severe malaria traditionally has been attributed mostly with *P. falciparum*, recent trends suggest that *P. vivax* has now emerged as a major cause of morbidity and mortality in infants and children [5, 6].

Data on the clinical and epidemiological profiles of children with severe malaria from urban centers in Northern India are limited and thus we analyzed the profile of severe malaria and contribution by *P. vivax* in it, among children who were admitted to a tertiary centre located in Patna, Bihar, India.

Material and Methods
Objective: To assess the clinical and epidemiological profiles of children with severe malaria and contribution of

Plasmodium vivax infection to malarial morbidity in North Indian children.

Study site. This prospective study was carried out at the Department of Pediatrics, Nalanda Medical College and Hospital (NMCH), Patna, Bihar, India from 1st January 2019 to 31st December 2019.

Enrolment

The study was conducted among children aged ≤ 15 years. Children with a short duration (< 7 days) of fever (temperature >100.4 °F) without any localized symptoms were screened from the pediatric outpatient and casualty.

Inclusion criteria: Children ≤ 15 years of age, diagnosed with severe malaria as per World Health Organization (WHO) (2014) criteria [7] were eligible to be included.

Exclusion criteria: Children whose parents refused to give the written consent or had other concurrent illness were not included in the study. Children with human immunodeficiency virus (HIV) infection, co-existing systemic illness (chronic renal failure, chronic liver disease, and known progressive neurological illness); and those who stayed in hospital for less than 6 hours were excluded.

The study protocol was fully explained to the parents/guardian, and written informed consent was obtained.

Study procedures. This study was conducted on children admitted with severe malaria in which the diagnosis was made by peripheral blood film (PBF) and/or rapid diagnostic test (RDT). Presence of malarial parasite on thick and thin smear stained with Giemsa stain and examined under oil immersion (slide was considered negative when there were no parasites in the 100 high-power fields) and/or positive p-LDH based rapid malaria antigen test was considered diagnostic of malaria. Parasite density was not estimated.

Patients were categorized into either of three groups: P. vivax (Pv) monoinfection, P. falciparum (Pf) monoinfection and mixed P. vivax with P. falciparum infection (Pf+Pv). Diagnosis of mixed infection was based on microscopic presence of gametocytes for P. falciparum along with presence of schizonts and trophozoites for P. vivax.

Apart from PBF and RDT, other laboratory investigations, which were done in all the patients of severe malaria, included complete blood count, platelet count, blood glucose, blood urea, serum creatinine, serum electrolyte, serum bilirubin (total and direct), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase, complete urine analysis, appropriate blood test to rule out enteric fever and dengue and arterial/venous blood gas.

Based on clinical indication other test were performed viz. reticulocyte count, prothrombin time, chest x-ray, fundus examination, cerebrospinal fluid (CSF) examination, computerized tomography (CT) of the head, electroencephalography (EEG), ultrasonography of whole abdomen, specific test for hepatitis B and C, glucose-6-phosphate dehydrogenase (G6PD) enzyme level and blood culture.

The demographic profile including the name, age, gender, and residential address, clinical features, and clinical course of illness were recorded.

Categorization of severe malaria and treatment was done according to World Health Organization (WHO) guidelines (2014) [7]. All information was collected on a standard proforma.

Antimalarial treatment was given in the hospital according to WHO guidelines (artesunate) along with other supportive treatment. Once it could be orally administered, children who were on IV artesunate were shifted to oral tablets of artemether + lumefantrine combination (3-day course). Need for pediatric intensive care unit admission was decided on a case to case basis.

Children were preferably admitted in the pediatric ward for a minimum of 7 days. However, if the parents insisted on an early discharge, they were asked to return for a follow-up at 7 days. We looked for improvement in fever (temperature < 100.4ºF for 24 hours), improvement in sensorium (GCS of 15/15 for a minimum of 24 hours), and improvement in thrombocytopenia (two records of platelet count collected more than 24 hours apart). Time to improvement in sensorium was defined as time to GCS of 15/15.

Statistical Analysis: All categorical variables were presented as proportions (%) and the comparison based on parasitological diagnosis was compared using chi square test. Continuous variables were presented as Mean (SD) or Median (IQR) in skewed distribution. The clinical features of severe malaria were compared among three groups viz, P. vivax (Pv) mono-infection, P. falciparum (Pf) mono-infection, and mixed Pv+Pf infection, by chi squared tests for categorical variables and ANOVA or Kruskal–Wallace testing for parametric or nonparametric data, respectively. Level of significance assumed in all tests was 5%. Statistical analysis was done using SPSS 22.0 version.

Results

In total, 1880 children were screened for malarial infection in our centre during the study period. Of these, 27 were diagnosed to be having severe malaria as per WHO definition [7]. 14 (51.8%) children were infected with P. vivax mono-infection, 8 (29.6%) with P. falciparum mono-infection, and 5 (18.5%) had mixed infection with both vivax and falciparum (Fig1).

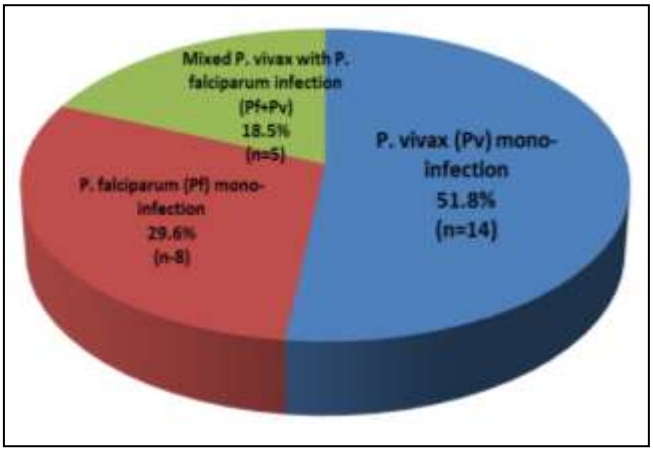

Fig 1: Severe malaria Incidence by Species.

Average age of these patient was 7.3 (± 3.5) years. The average age [age in years (± SD)] was comparable among P. vivax [6.83 (4.19)], P. falciparum [7.27 (3.75)], and Mixed infection group [7.54 (4.76)]. Among 27 enrolled patients

19 (70.3%) were male and 8 (29.7%) were female. Male–female ratio was similar with male predominance in all the groups. Among 14 children diagnosed with P. vivax mono-infection, 5 children were under 5 years of age, 5 in the age group of 5–10 years, and 4 were above 10 years of age (Table 1).

Table 1: Demographic profiles of children with severe malaria

Characteristics of patients	P. vivax mono-infection (n=14)	P. falciparum monoinfection (n=8)	Mixed Pf +Pv (n=5)	Total (n=27)
Sex distribution				
Male	11 (78.5%)	5 (62.5%)	3 (60%)	19 (70.3%)
Female	3 (21.5%)	3 (37.5%)	2 (40%)	8 (29.7%)
Age range (years)				
0-5	5 (5/14, 35.7%)	1 (1/8, 12.5%)	1 (1/5, 20%)	7 (7/27, 25.9%)
5-10	5 (5/14, 35.7%)	4 (4/8, 50%)	2 (2/5, 40%)	11 (11/27, 40.7%)
>10	4 (4/14, 28.5%)	3 (3/8, 37.5%)	2 (2/5, 40%)	9 (9/27, 33.3%)
Duration of illness				
Median	7	5	6	6
Range	3-22	4-28	4-25	
Duration of hospitalization				
Median	6	5	6	6
Range	1-24	1-34	1-28	
Mortality	3	1	1	5

Fever was the chief presenting complaint in all the patients [n=27, (100%)], with a median duration of 6 (range 2-9) days. Other clinical presentation were headache [21 (77.8%)], vomiting [10 (37.03%)], diarrhea [4(14.8%)], seizures [11(40.7%)], impaired consciousness [14 (51.85%)], abnormal behavior [6 (22.2%)] and bleeding [1 (3.7%)] (Table2). The clinical signs among these patients included hepatomegaly [22 (81.48%)], splenomegaly [25 (92.6%)], pallor [22 (81.4%)], icterus [5 (18.5%)], and respiratory distress [2 (7.4%)]. Out of 27 severe malaria patients, 7 (25.9%) patients with severe anemia (hemoglobin <5 g/dL) required blood transfusion. Thrombocytopenia (platelet <1.5 lakhs/dL) was observed in 18 (66.7%) children while acute renal failure (serum creatinine >1.5 mg/dL) was seen in 5 (18.5%) cases. Blood culture in 25 children and urine cultures all were sterile.

Table 2: Clinical and laboratory profile of severe malaria

Clinical and laboratory features of severe malaria				
	P. vivax Mono-infection (n=14)	P. falciparum monoinfection (n=8)	Mixed Pf +Pv (n=5)	Total (n=27)
Symptoms				
Fever	14 (100%)	8 (100%)	5 (100%)	27 (100%)
Headache	10 (71.4%)	6 (75%)	5 (100%)	21 (77.8%)
Vomiting	8 (57.1%)	1 (12.5%)	1 (20%)	10 (37.03%)
Diarrhoea	2 (14.2%)	1 (12.5%)	1 (20%)	4 (14.81%)
Impaired consciousness	9 (64.2%)	2 (25%)	3 (60%)	14 (51.85%)
Seizure	5 (35.7%)	3 (37.5%)	3 (60%)	11 (40.7%)
Abnormal behaviour	3 (21.4%)	2 (25%)	1 (20%)	6(22.2%)
Signs				
Pallor	11 (78.57%)	7 (87.5%)	4 (80%)	22 (81.4)
Icterus	3 (21.4%)	1 (12.5%)	1 (20%)	5 (18.5%)
Hepatomegaly	11 (78.5%)	7 (87.5%)	4 (80%)	22 (81.48)
Spleenomegaly	13 (92.8%)	7 (87.5%)	5 (100%)	25 (92.6%)
Bleeding	1 (7.1%)	0	0	1 (3.7%)
Respiratory distress	2 (14.2%)	0	0	2 (7.4%)
Shock	1 (7.1%)	3 (37.5%)	1 (20%)	5 (18.5%)
Lab. Parameters				
Severe anemia (Hb < 5g/dl)	3 (21.4%)	5 (62.5%)	2 (40%)	10 (37%)
Thrombocytopenia	8 (57.1%)	6 (75%)	4 (80%)	18 (66.6%)
Renal imapirment	3 (21.4%)	1 (12.5%)	1 (20%)	5 (18.5%)
Hepatic Dysfunction	3 (21.4%)	1 (12.5%)	1 (20%)	5 (18.5%)

Diagnosis of P. vivax monoinfection was made in 14 children of whom 4 (28.5%) were diagnosed positive by rapid antigen test, 7 (50.0%) were positive by smear examination, and 3 (21.4%) were positive by both (table 3).

Table 3: Severe malaria incidence by species and investigation

Severe malaria	Only Peripheral Blood Film (PBF)	Only Rapid Diagnostic Test (RDT)	Both PBF + RDT	Total
P. falciparum mono infection	4 (50%)	3 (37.5%)	1 (12.5%)	8 (29.6%)
P. vivax mono-infection	7 (50%)	4 (28.5%)	3 (21.4%)	14 (51.8%)
Mixed infection (Pf+ Pv)	3 (60%)	0	2 (40%)	5 (18.5%)
Total severe malaria patients	14 (51.8%)	7 (25.9%)	6 (22.2%	27

The age of the patients with severe vivax malaria (n=14) ranged from 9 months to 14 years; 11 (78.5%) of them were male. Clinical examination findings in children infected with P. vivax were pallor [11 (78.5%)], icterus [3 (21.4%)], hepatomegaly [11 (78.5%)], and splenomegaly [13 (92.8%)]. 8 (57.1%) children with P. vivax monoinfection had more than one manifestation of severe malaria. 9 out of theses 14 children presented with encephalopathy, among these, 5 had multiple convulsions, 3 had severe anemia requiring blood transfusion, and 1 had spontaneous bleeding (Table2). Lumbar puncture was done in 8 of the 9 children presenting with altered sensorium, which were all acellular with normal cerebrospinal fluid biochemical parameters.

All 14 (100%) children with P. vivax monoinfection were initiated on intravenous artesunate followed by a 3-day course of artemether-lumefantrine combination therapy once the patient could be allowed oral medications.

3 [3/14 (21.4%)] children infected with P. vivax monoinfection died. The outcome was favorable (survival at 7 days) among the other 11 (78.5.7%) children. However, one [1/8 (12.5%) child diagnosed as cerebral malaria due to *P. falciparum* associated infection died within a few hours of hospitalization. One [1/5 (20%)] child with mixed infection died on day 2.

The duration of hospitalization was more than 7 days in 8 children [8/27 (29.6 %)]. More than half of the children with P. vivax infection [8/14 (57.1%)] had improvement in fever in 2–5 days time frame. Among children with P. vivax monoinfection cerebral malaria, 6 [6/9 (66.6%)] children had improvement in sensorium within 48 hours.

Among smear positive P. vivax monoinfection, parasitemia clearance took 48 hours in 21.4%; 5 days in 57.1% and 21.4% had cleared by 7 days.

Antibiotics were initiated in all children pending the blood culture report. The cultures were sterile after 48 hours of incubation in 25 children and the antibiotics were omitted following a sterile culture report.

Pv patients had much wider age range compared to Pf though median age was similar in both groups. However, proportion of patients from younger age group (<5 y) was significantly higher in Pv group. Duration of illness and hospitalization were also similar in both groups with shorter median duration of symptoms in Pf group.

Among various clinical syndromes, severe anemia, cerebral malaria and hepatitis were most common in both groups.

Severe anemia and shock were more frequently observed in Pf group whereas cerebral malaria, Hepatitis, ARF, acute respiratory distress syndrome (ARDS) and bleeding symptoms were more commonly seen in Pv patients.

Among hematological parameters, severe anemia (Hb <5 g/dl) was significantly more common in Pf group and more frequently required packed red cell transfusions. Thrombocytopenia was common in Pv group, though no significant difference was observed in occurrence of severe thrombocytopenia and platelet transfusion requirement in both groups. Mortality was highest in Pv mono-infection mixed. Most of these patients had 2 or more clinical syndromes simultaneously. Cerebral malaria was most common cause of mortality (3 cases), followed by DIC (1), shock (1).

Discussion

Malaria is one of the major public health problems in India with infants, young children, and pregnant women being high-risk groups to develop severe malaria. In 2017, National Vector Borne Disease Control Programme (NVBDCP) reported around 0.84 million confirmed cases of malaria. Out of these, 0.53 million cases were due to P. falciparum. *P. vivax*, however, is now being regarded as an important causative agent in cases of severe malaria.

In this study, 51.8% cases of severe malaria were due to P. vivax mono-infection, while P. falciparum mono-infection contributed for only 29.6%, with mixed infections being identified in 18.5% case. *P. vivax* malaria initially was considered to be benign malaria with a very low case-fatality ratio; however its recent emergence as causative agent of severe malaria could have significant implications in the management of malaria in northern India.

This study indicates that the clinical features and outcome of severe vivax malaria is similar to severe falciparum malaria, except for higher chances of severe anaemia among the latter.

Findings on severe vivax malaria in this study are consistent with those reported from Papau New Guinea and Indonesia [8, 9]. In recent years *P. vivax* has emerged as important causative agent in cerebral malaria [10]. P. vivax is now being identified as an important cause of severe malaria in children with clinical manifestations like cerebral malaria, anaemia, and thrombocytopenia. Other manifestations of severe vivax malaria include respiratory distress, coma, malnutrition, splenic rupture, and acute renal failure and shock.

Cerebral malaria, severe anaemia, and thrombocytopenia as features of severe vivax malaria in our study is in agreement with study from Delhi and Bikaner [10, 11].

In our study P. vivax mono-infection accounted for 51.8 % cases of severe malaria. In a large prospective study from Bikaner district of North India, P. vivax monoinfection contributed to one third of cases [11]. In that study, patients with vivax monoinfection had a higher incidence of severe anaemia, cerebral malaria, acute respiratory distress syndrome, hepatic and renal dysfunction. In one study from Delhi, it was observed that severe anaemia and shock were more frequent among children infected with P. falciparum [10]. These results were consistent with our findings of severe anaemia among P. falciparum group.

Cerebral malaria is characterised by sequestration of infected red blood cells in cerebrovascular system. Kochar *et al.* showed that cerebral malaria by P. vivax can be due to both sequestration-related and non-sequestration-related mechanism [11].

Severe thrombocytopenia though a common manifestation of P. *falciparum* malaria is not uncommon in *P. vivax* malaria [12]. It could be attributed to either direct lysis of platelets by *P. vivax* or by immunological destruction by platelet-associated IgG antibody oxidative stress damage of thrombocytes. 66.6% of our total patients had thrombocytopenia. Study by Yadav *et al* [10] reported thrombocytopenia in 83.2% cases with P. vivax malaria, with 13 requiring platelet transfusion. In a large prospective study from the Bikaner district of North India, incidence of thrombocytopenia was 73.16% (278/ 380) of children with P. vivax monoinfection, 55.34% in P. falciparum monoinfection and 55.88% in mixed infection. In contrast, our study saw 57.14% (8/ 14) of the P. vivax severe malaria cases having low platelet count.

Severe anaemia is usually a common feature of severe falciparum malaria which could be due to destruction of

parasitized red cells, complement mediated lysis, phagocytosis of non-parasitized red cells, increased splenic clearance, reduction of red cell survival, dyserythropoeisis or drug induced hemolysis.

In the present study, all 27 children were started on intravenous artesunate and then switched to course of artemether-lumefantrine combination when they are able to tolerate oral drugs.

Reasonable clinical improvement with no evidence of early or late treatment failures was seen in most cases. Moreover, the majority of the children had improvement in fever, sensorium with return of normal platelet count by the sixth day of admission.

Limitation of this study is being a single centre study conducted in a tertiary level hospital with limited sample size.

To conclude, our study highlights P. vivax as an increasingly recognized causative agent for severe malaria in children from Bihar, northern India with a similar clinical presentation and outcome to that caused by P. falciparum.

However, a larger sample size and a longer follow-up period would be reasonable to predict the outcome of this emerging trend

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